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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Appellants : Josephus Brugmans, et al.

Serial No. : 230,578

Filed : February 2, 1981

For : AIDING THE REGRESSION OF NEOPLASTIC DISEASE WITH 2,3,4,6-TETRAHYDRO-6-PHENYLIMIDAZO (2,1-b) THIAZOLE

Examiner : Jerome D. Goldberg

Group : 125

620-40

BRIEF ON BEHALF OF JOSEPHUS BRUGMANS, ET AL.

GEOFFREY G. DELLENBAUGH
FOR APPELLANTS

Commissioner of Patents and Trademarks
Washington, D.C. 20231

August 5, 1983

Dear Sir:

This is an appeal from the Final Rejection of Claims 1-19, dated February 25, 1983. An Oral Hearing is not requested. Three copies of this Brief are being furnished for the convenience of the Honorable Board.

THE INVENTION

Appellants have discovered a method of aiding the regression and palliation of neoplastic disease by systemically administering to a diseased subject an effective antineoplastic amount of the chemical compound tetramisole or its levo isomer levamisole.

Prior art chemotherapeutic anticancer agents have acted principally by selective poisoning of neoplastic tissue. Thus, these materials have had severe side effects and are in fact used by the medical profession only because of the seriousness of the disease and because of the unavailability of better therapies. Such side effects manifest themselves as

nausea, vomiting, hair loss, and increased susceptibility to infection due to the destruction of rapidly dividing normal body cells such as hair follicles, cells lining the gastrointestinal tract, and bone marrow cells involved in the immune defense system. Such chemotherapeutic agents are exemplified by the antimetabolites such as methotrexate, alkylating agents such as the nitrogen mustard compounds, and antibiotics such as adriamycin.

By contrast to these prior art chemotherapeutic agents, the present invention provides for the first time a material which acts by stimulating the body's own immune system to reject the neoplasm, rather than by selective poisoning of the neoplastic tissue.

THE CLAIMS

The claims on appeal read as follows:

1. A process of aiding regression and palliation of neoplastic disease which comprises the systemic administration to human and animal subjects hosting the neoplastic disease of an effective antineoplastic amount of a member selected from the group consisting of 2,3,5,6-tetrahydro-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof in a pharmaceutical carrier.

2. A process of aiding regression and palliation of neoplastic disease which comprises the systemic administration to a human hosting the neoplastic disease of from about 1 to about 5 mg/kg body weight of the host of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof.

3. A process of aiding regression and palliation of pulmonary metastatic tumor which comprises the systemic

administration to a or animal host of said tumor of an effective tumor-inhibiting amount of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo-[2,1-b] thiazole and the therapeutically active acid addition salts thereof in a pharmaceutical carrier.

4. A process of aiding regression and palliation of breast cancer which comprises the systemic administration to human or animal subjects hosting breast cancer of an effective antineoplastic amount of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof in a pharmaceutical carrier.

5. A process of aiding regression and palliation of breast cancer which comprises the systemic administration to a human hosting breast cancer of from about 1 to about 5 mg/kg body weight of the host of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof.

6. A process of aiding regression and palliation of lung cancer which comprises the systemic administration to human or animal subjects hosting lung cancer of an effective antineoplastic amount of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof in a pharmaceutical carrier.

7. A process of aiding regression and palliation of lung cancer which comprises the systemic administration to a human hosting lung cancer of from about 1 to about 5 mg/kg body weight of the host of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b]

thiazole and the therapeutically active acid addition salts thereof.

8. A process of aiding regression and palliation of malignant melanoma which comprises the systemic administration to human or animal subjects hosting malignant melanoma of an effective antineoplastic amount of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof in a pharmaceutical carrier.

9. A process of aiding regression and palliation of malignant melanoma which comprises the systemic administration to a human hosting malignant melanoma of from about 1 to about 5 mg/kg body weight of the host member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof.

10. A process of aiding regression and palliation of colorectal cancer which comprises the systemic administration to human or animal subjects hosting colorectal cancer of an effective antineoplastic amount of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof in a pharmaceutical carrier.

11. A process of aiding regression and palliation of colorectal cancer which comprises the systemic administration to a human hosting colorectal cancer of from about 1 to about 5 mg/kg body weight of the host of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof.

12. A process of aiding regression and palliation of multiple myeloma which comprises the systemic administration to human or animal subjects hosting multiple myeloma of an effective antineoplastic amount of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof in a pharmaceutical carrier.

13. A process of aiding regression and palliation of multiple myeloma which comprises the systemic administration to a human hosting multiple myeloma of from about 1 to about 5 mg/kg body weight of the host of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof.

14. A process of aiding regression and palliation of head and neck cancer which comprises the systemic administration to human or animal subjects hosting head and neck cancer of an effective antineoplastic amount of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof in a pharmaceutical carrier.

15. A process of aiding regression and palliation of head and neck cancer which comprises the systemic administration to a human hosting head and neck cancer of from about 1 to about 5 mg/kg body weight of the host of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof.

16. A process of aiding regression and palliation of bladder cancer which comprises the systemic administration to

human or animal subjects hosting bladder cancer of an effective antineoplastic amount of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof in a pharmaceutical carrier.

17. A process of aiding regression and palliation of bladder cancer which comprises the systemic administration to a human hosting bladder cancer of from about 1 to about 5 mg/kg body weight of the host of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof.

18. A process of aiding regression and palliation of gastric cancer which comprises the systemic administration to human or animal subjects hosting gastric cancer of an effective antineoplastic amount of a member selected from the group consisting of 2,3,5,6,tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof in a pharmaceutical carrier.

19. A process of aiding regression and palliation of gastric cancer which comprises the systemic administration to a human hosting gastric cancer of from about 1 to about 5 mg/kg body weight of the host of a member selected from the group consisting of 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole and the therapeutically active acid addition salts thereof.

THE FINAL REJECTION

Claims 1-19 have been rejected under 35 USC 101 on the ground that the evidence of record is insufficient to demonstrate the utility of the claimed methods for all types of cancer in both humans and animals, citing the decision of In re Buting, 163 USPQ 689 (CCPA 1969).

Claims 1-19 have also been rejected under 35 USC 112 (first paragraph) on the ground that the terms describing the neoplastic disease being treated lack clear exemplary support in the specification.

THE ISSUES

I. Whether the evidence of record demonstrates the utility of the rejected claims as required by 35 USC 101.

II. Whether the specification enables any person skilled in the cancer treatment art to practice the invention described in the rejected claims as required by 35 USC 112 (first paragraph).

APPELLANTS' ARGUMENTS

Appellants respectfully submit that the rejections appealed from are improper and request the rejected claims be granted to them for the reasons presented below.

A. Background

Although the claims have been rejected under both 35 USC 101 and 35 USC 112 (first paragraph), the main issue herein is whether Appellants have submitted sufficient evidence to establish their asserted utility of the rejected method claims. In this regard, the appealed claims are believed to be closely similar in character to those at issue in the case of In re Jolles, 206 USPQ 885 (CCPA 1980).

Appellants' parent application SN 067,505 was also the subject of an appeal to this Honorable Board from the identical rejections of claims 1-3 (claims 4-19 not being present in the parent application). In support of the utility of the rejected claims, Appellants then relied upon an article entitled "Effects of Levamisole Treatment in Cancer Patients" authorized by Willem K. Amery and Hermen C. Verhaegen (the "Amery article") reviewing the results of clinical studies

practicing the rejected methods. In its decision, the Honorable Board affirmed the Examiner's 35 USC 101 rejection based on the insufficiency of the evidence presented by Appellants. The Board stated that the Examiner should have an opportunity to independently review the primary sources on which the Amery article was based. The Board held that the Examiner's 35 USC 112 rejection was subsumed within the 35 USC 101 rejection and stated that it would consider probative evidence of the scope of the Amery article to support the term "neoplastic disease" generally.

In the present application, Claims 1-3 have been refiled and new claims 4-19 have been added directed to methods of treating specific neoplastic diseases set out in the Amery article. Additionally, the primary sources upon which the Amery article was based have been provided to the Examiner in the belief that such evidence would cause him to allow the claims. Despite this probative evidence, the Examiner has finally rejected all of the pending claims.

B. The Evidence of Record Demonstrates the Utility of the Appealed Claims

At the filing of the subject application, Appellants submitted the Amery article and the "Updated Clinical Summary - 1980" from the amended New Drug Application for levamisole.

In response to the initial rejection of the subject application, Appellants further submitted the primary sources upon which the Amery article was based. Since the Examiner has not questioned the truth of the results reported in the Amery article or the primary sources, the dispositive issue is therefore whether the proofs contained in this article and the primary sources are sufficient to establish the utility of the appealed claims. For the convenience of the Honorable Board,

a photocopy of the Amery article is attached hereto as Exhibit A. The extensive primary sources may be found in the application file.

Even a casual examination of the Amery article reveals the extensive amount of clinical research which has been conducted on cancer patients using levamisole. As stated in the section entitled "The Available Experience" beginning on the first page of the article (page 123), the studies reported include 1,474 levamisole-treated patients as well as about 1,600 controls. A large variety of neoplastic diseases were studied, including breast cancer, lung cancer, colorectal and/or other digestive cancers, leukemias and lymphomas, malignant melanoma, head and neck carcinoma, and bladder cancer. These controlled studies are summarized in Table 1 at page 132 of the article, which indicates not only the large variety of neoplastic diseases which were studied but also the many different types of primary treatment with which levamisole treatment was combined.

It is Appellants' position that the results contained in the Amery article and the primary sources, as well as in the Application, are convincing evidence accepted by those skilled in the art that levamisole possesses the claimed utility. Nothing more is required. In re Irons, 144 USPQ 351 (1965).

Based upon this evidence, it is respectfully submitted that one of ordinary skill in the cancer-treatment art would be convinced that levamisole is useful in a "process of aiding regression and palliation of neoplastic disease which comprises the systemic administration to human and animal subjects hosting the neoplastic disease of an effective antineoplastic amount of [tetramisole or levamisole]...".

In his rejection, the Examiner has not called into question the validity of any of the data which have been submitted. Rather, based upon the authority of In re Buting, supra, he has asserted that the evidence is insufficient. It is respectfully submitted, however, that the Examiner's position is not supported by Buting.

In Buting, the Court of Customs and Patent Appeals (as it then was) rejected claims directed to treatment of a variety of neoplastic diseases on the ground that insufficient evidence had been presented to support the broad utility claimed. The Buting evidence was treatment of two types of cancer in one patient each with one compound, while the claims were directed to the treatment of seven types of cancer with several compounds. It appears that the Court did not consider the animal test data to be probative of utility in humans. The Court implied that the clinical evidence would be sufficient to support a claim limited to the one compound and two types of cancer tested.

Appellants have submitted evidence of treatment of 1,474 patients. For the Examiner to rely for his rejection on Buting (where two patients were treated) seems highly inappropriate.

Moreover, the continued vitality of Buting is called into serious doubt by the recent decision of In re Jolles, supra, in which the dispositive issue was identical to that presented herein.

In Jolles, evidence of clinical treatment of 100 patients having acute myeloblastic leukemia with one of the claimed compositions (resulting in complete remission in 53) was considered sufficient to support a claim to a method of treatment of this disease with that composition. In addition,

tests of related compositions in rats having various experimental tumors were held to supplement the clinical testing sufficiently to satisfy the utility requirement with regard to these related compositions.

The Examiner's remarks in Paper No. 5 that the data of record are" ...obviously no substitute for a showing of such utility by proper evidence in both humans and animals, with statistically significant data, based on all tests conducted" is taken to be factually incorrect. The data of record constitute a showing of utility for levamisole in a wide variety of different neoplastic diseases in animals and (most particularly) humans. These data are statistically significant, as can be seen (for example) from the discussion under the heading "The More Advanced Studies" on page 124 of the article. At this point, the Amery article states:

> "All studies have produced a trend to the advantage of levamisole, at least in a subgroup of patients (see further), that reached the level of statistical significance in thirteen of the seventeen studies."

Moreover, examination of the reports of the primary sources summarized in this reference clearly indicates the statistical significance of the data.

Finally, the Amery article (as well as most of the primary sources summarized therein) were published in reputable, refereed journals and accepted by those of ordinary skill in the art as indicating the truth of what was stated therein. It is therefore respectfully submitted that the utility disputed by the Examiner is in fact already accepted by the very audience to whom this patent application is directed: i.e., those skilled in the cancer treatment art. Since the Examiner has the primary sources available to him,

he is able to make an independent review of the studies relied on by Appellants.

In the subject application, Appellants are claiming the use of a single compound (tetramisole or its levo isomer levamisole) in aiding regression of neoplastic disease generally and specific neoplastic diseases. Evidence has been presented of utility in a large variety of neoplastic diseases in humans and in a variety of experimental tumors in mice. The primary sources referred to in the Amery article are of record. Under the rationale of Jolles, one of ordinary skill in the art would accept Appellants' claimed utility in humans and animals as valid and correct.

C. The Specification Enables the Practice of the Rejected Claims

With regard to the rejection under 35 USC 112 (first paragraph), the Examiner has stated that the term "neoplastic disease" in Claims 1 and 2 and the terms relating to specific diseases in Claims 3-19 lack clear exemplary support in the specification and that moreover the data of record are insufficient to support a claim to treatment of "neoplastic disease" broadly.

The relevant portion of the first paragraph of 35 USC 112 requires only that the disclosure enable one skilled in the art to practice the invention. It is respectfully submitted that the disclosure of the specification as supplemented by the evidence of record fulfills this requirement.

Initially, the Honorable Board's attention is respectfully directed to the first paragraph on page 3 of the specification in which the term "neoplastic disease" is defined to include broadly all types of cancerous growths or oncogenic processes, and the like. The specification also

describes the preparation of suitable pharmaceutical compositions and indicates a dosage range. Thus, the specification clearly enables the practice of the claimed invention.

The evidence of record, it is respectfully submitted, clearly demonstrates that those of ordinary skill in the art do indeed know precisely how to practice the subject invention and are in fact doing so quite readily. All of the advanced studies reported in the Amery article and the primary sources have produced a trend to the advantage of levamisole in a wide variety of types of neoplastic disease. Moreover, the early stage reports are at worst inconclusive, while several of them have shown results which may be helpful.

Since the entire foundation of this rejection is contradicted by the evidence of record, the rejection should be reversed.

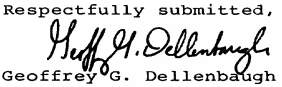
This Honorable Board recognized in its decision in Appellants' parent application the sufficiency of the evidence of record (including the primary sources of the Amery article) to support the presently claimed scope.

D. Summary

Appellants have discovered a method of aiding the regression and palliation of neoplastic disease by systemically administering to diseased subjects an effective neoplastic amount of tetramisole or levamisole. This is a significant advance in the art since, for the first time, a material is available which acts by stimulating the body's own immune system to reject the neoplasm rather than by selective poisoning of neoplastic tissue. Appellants have demonstrated that the subject claims comply with all requirements of the patent statutes and especially with 35 USC 101 and 35 USC 112.

Accordingly, the Honorable Board is respectfully requested to reverse the decision of the Primary Examiner and to grant to Appellants the claims on appeal.

Respectfully submitted,



Geoffrey G. Dellenbaugh
Attorney for Appellants
Registration No. 26,864

GGD/dd
August 5, 1983

One Johnson & Johnson Plaza
New Brunswick, N.J. 08933-7003
(201) 524-5545

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Josephus Brugmans, et al.	)	Group: 120
Serial No.:	230,578	)	Examiner: J. Goldberg
Filed :	February 2, 1981	)	
For :	AIDING THE REGRESSION OF NEOPLASTIC DISEASE WITH 2,3,4,6-TETRAHYDRO-6-PHENYLIMIDAZO (2,1-b) THIAZOLE	)	

Honorable Commissioner of
Patents & Trademarks
Washington, D.C. 20231

REPLY BRIEF ON BEHALF OF JOSEPHUS BRUGMANS, ET AL.

GEOFFREY G. DELLENBAUGH
FOR APPELLANTS

Dear Sir:

This Reply Brief responds to the new points of argument raised in the Examiner's Answer dated January 9, 1984.

In his Answer, the Examiner has allowed claims 13-16, 18, and 19. He has also withdrawn his rejection of claim 17 under 35 U.S.C. 112.

In support of his continued rejection of claims 1, 2, and 17 under 35 U.S.C. 101 and claims 1 and 2 under 35 U.S.C. 112 (first paragraph) the Examiner has cited certain portions of the Smith, et al. publication (Cancer Treatment Reports, Volume 62, No. 11, November 1978) of record and concludes that "this data obviously would not support the treatment of bladder cancer with levamisole."

Appellants wish to observe that if the Examiner is concerned about support for claims to treatment of bladder cancer, his allowance of claim 16 (which is directed to such treatment) must have been in error. Appellants will assume, for purposes of this Reply Brief, that the rejected claims are actually 1, 2, 16, and 17.

Appellants have cancelled claims 16 and 17 to narrow the issues on appeal but respectfully submit that the Examiner's continued rejection of claims 1 and 2 should be reversed.

The authors of the Smith, et al. publication referred to by the Examiner describe it as a preliminary report and begin their Discussion section by saying:

> "The number of patients and length of follow-up are obviously too small to permit any statements with regard to the efficacy of levamisole as an immune adjuvant in the treatment of bladder cancer."

Appellants recognize that the results in the Smith, et al. publication (which is the only publication of record dealing with bladder cancer) are inconclusive as to the effect of levamisole in treatment of bladder cancer. Accordingly, Appellants have cancelled claims 16 and 17.

Appellants respectfully submit, however, that claims 1 and 2, directed to methods of treating neoplastic disease generally, should be granted to them. The evidence of record demonstrates that levamisole is useful in treating a large variety of neoplastic diseases, including pulmonary metastatic

tumor, breast cancer, lung cancer, malignant melanoma, colorectal cancer, multiple myeloma, head and neck cancer, and gastric cancer. The Examiner has recognized the sufficiency of the showing with respect to these specific diseases by allowing claims directed to the treatment thereof.

With respect to bladder cancer, the one preliminary study which is of record does not allow one to determine whether levamisole is or is not effective. Appellants wish to emphasize, however, that the Smith, et al., publication does not present negative results, it simply presents inconclusive results. Appellants vigorously dispute the Examiner's contention that the Smith, et al. reference demonstrates that levamisole is "ineffective" in the treatment of bladder cancer.

Despite this inconclusive preliminary result for treatment of bladder cancer, the fact that levamisole has been demonstrated effective to treat eight different types of neoplastic disease is sufficient to convince one skilled in the art that levamisole is generally useful to treat neoplastic disease as required by 35 U.S.C. 101 and to teach one skilled in the art how to practice the methods of claims 1 and 2 as required by 35 U.S.C. 112 (first paragraph).

Considered as a whole, the data of record are convincing to one skilled in the cancer-treatment art that the methods of claims 1 and 2 are useful. Such a skilled person would recognize that the Smith, et al. publication, reporting preliminary results, is simply inconclusive and would not

conclude from it that levamisole would be ineffective to treat any neoplastic disease, including bladder cancer. The inconclusive nature of the Smith, et al. publication is clearly outweighed by the 26 other articles reporting successful treatment of eight other types of neoplastic disease with levamisole.

With regard to the rejection under 35 U.S.C. 112 (first paragraph), method claims 1 and 2 are sufficiently enabled by the specification to allow any person skilled in the cancer-treatment art to practice these methods. As stated previously, the fact that the term "neoplastic disease" may lack clear exemplary support in the specification as filed is irrelevant in view of the current state of the record.

For the above reasons, this Honorable Board is respectfully requested to reverse the Examiner's rejection of claims 1 and 2 (the only rejected claims still pending in the present appeal) and to grant these claims to Appellants.

Respectfully submitted,

Geoffrey G. Dellenbaugh
Attorney for Appellants
Registration No. 26,864

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(201) 524-5545
January 25, 1984

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D. C. 20231, on January 25, 1984
(Date of Deposit)
Geoffrey G. Dellenbaugh (Reg. # 26,864)
Name of applicant, assignee, or Registered Representative

(Signature)

January 25, 1984
(Date of Signature)